REMARKS

Reconsideration of the present Application is respectfully requested in view of the Amendment submitted herewith and the following remarks. Further to the Advisory Action mailed by the PTO on January 2, 2004, Applicants' Amendment, which was filed on December 3, 2003, in response to the Final Office Action dated June 3, 2003, was not entered into the record. A Notice of Appeal was also filed on December 3, 2003, and in lieu of an Appeal Brief, a Request for Continued Examination is enclosed herewith.

Accordingly, and upon entry of the present Amendment, claims 22, 24-39, and 44-63 are currently pending. Applicants acknowledge the Examiner's notation in the Office Action dated June 3, 2003, that the Appendix of Currently Pending Claims submitted by Applicants with the Response previously filed March 4, 2003, did not include claim 31. Applicants submit that omission of claim 31 was an inadvertent error, and the claim is included in the present Listing of the Claims that begins on page 2 of this paper. Claims 21 and 41-43 are hereby canceled according to the present Amendment, without acquiescence in any rejection and without prejudice to the prosecution of any encompassed subject matter in a related continuation, continuation-in-part or divisional application. Applicants have added new claims 61-63 to define more clearly the subject matter encompassed by Applicants' invention. Claims 22, 32, 37, 44, 45, and 52-56 have been amended solely to correct their dependencies in view of the cancellation of claims 41-43.

Support for the amended claims submitted herewith may be found in the specification, for example, at page 4, lines 24-34; at page 9, line 32 through page 10, line 7; and at page 17, line 18 through page 18, line 22; and elsewhere. In addition, support for the amended claims submitted herewith may be found in the specification, for example, at page 4, lines 24-29; at page 17, lines 18-24; at page 21, lines 35-36; in originally filed claim 2; at page 9, line 31 through page 10, line 2; at page 16, lines 31-36; at page 17, lines 28-32; at page 4, lines 29-32; at page 17, line 34 through page 18, line 22; at page 19, lines 3-8; at page 10, lines 3-7; at page 4, lines 32-34; at page 18, line 29 through page 19, line 1; at page 20, lines 4-11; at page 24, lines 9-14; at page 21, lines 1-7. No new matter has been added.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (WRITTEN DESCRIPTION)

In the Final Office Action dated June 3, 2003, the PTO rejects claims 21-22, 24-37, and 41-60 under 35 U.S.C. § 112, first paragraph, alleging that the claims are directed to subject matter that is not adequately described in the specification. The Action alleges that the recitation "wherein the first fraction has not been subjected to a method for isolating a cancer cell", and the reference in the claims to detection in a non-cancer cell from the subject of the second nucleic acid of step (c), constitute new subject matter that is not supported by the specification.

Applicants respectfully traverse this rejection and submit that Applicants possessed the claimed invention, as disclosed in the specification and recited in the instant claims, at the time the Application was filed, and that no new subject matter has been added. As an initial matter, Applicants point out that claims 21 and 41-43 have been canceled by the present Amendment without acquiescence to any rejection and without prejudice to future examination of any encompassed subject matter, rendering moot the rejections of these claims.

Applicants' invention is directed to a method for determining an increased risk for or presence of a disseminated cancer cell or a micrometastasizing cancer cell in a body fluid from a subject, comprising in pertinent part (a) investigating, in a plurality of cells obtained from a body fluid of a subject as recited, for at least one first nucleic acid that is a first cancer-specific nucleic acid or a first cancer-associated nucleic acid, wherein either (i) the step of investigating takes place without previous removal of cancer cells from the plurality of cells, (ii) the first nucleic acid is a first cancer-specific or cancer-associated mRNAthat is essentially not expressed in a non-cancer cell in the body fluid, or (iii) both (i) and (ii); (b) isolating at least one cancer cell from the body fluid as recited; (c) investigating at least one such isolated cancer cell for a second nucleic acid that is a second cancer-specific or a second cancer-associated nucleic acid; and (d) investigating at least one non-cancer cell from the body fluid for at least one second nucleic acid of step (c), as recited.

Contrary to the position articulated by the PTO at pages 3-4 of the June 3, 2003, Office Action, the application clearly teaches embodiments wherein the recited step of investigating "may take place without previous removal of the cancer cells" (*e.g.*, specification, at page 21, lines 35-36). The specification also discloses that body fluids "can be analyzed in the

state in which they have been obtained" (page 17, lines 18-19), which would not convey to a person skilled in the art that a step of removing cancer cells had been performed.

Additionally, the PTO clearly errs in asserting that the "specification does not appear to provide a single example teaching isolating cancer cells in one fraction and NOT isolating cancer cells in a separate fraction" (Action, page 4, lines 10-12, emphasis in original), and in alleging that only a single passage in the specification contemplates a "two assay" method. On the contrary, Applicants submit that the specification is rife with examples describing the presently claimed invention. The PTO concedes that the specification teaches, at page 31, the isolation of "fraction A which was not enriched for cancer cells" (Action, page 4, line 8). The PTO appears to have overlooked, however, a description in the specification of "fraction A", for example, as "MNC including the tumor cells", and also a description therein of "fraction C" as, *e.g.*, "purified tumor cells", for instance, at page 18, lines 30-32.

Moreover, the specification provides multiple examples comparing, within the same example, the PCR analysis of several cancer-specific or cancer-associated nucleic acids in whole blood (*e.g.*, whole blood mononuclear cells (MNC), *i.e.*, "fraction A") and in "fraction C" isolated therefrom. For instance, at page 47, lines 11-14, the specification teaches that "[t]he analysis is carried out *both* in whole blood, which reflects the ratio of alleles in normal cells, *and* in fraction C which representatively indicates the condition of the cancer cells" (emphasis added). At page 51, lines 27-28, results are presented from investigation for MUC1 mRNA in whole blood from a breast carcinoma patient and in isolated "fraction C" cancer cells therefrom. At page 53, lines 22-25 present data comparing the results of investigation of whole blood from a patient suspected of having colon or prostate carcinoma and of "fraction C" cancer cells isolated therefrom, for EGP mRNA and for GAPDH mRNA. Similar comparisons can be found elsewhere in the specification, for example, at page 56, lines 10-11, at page 57, line 35 and page 58, line 15 (MUC1 mRNA in unfractionated body fluid cells and in fraction C); at page 58, lines 11 and 13 (EGP mRNA in unfractionated cells and in fraction C); at page 58, lines 12 and 14 and page 60, lines 7 and 9 (GAPDH mRNA); and at page 57, line 36 and page 58, line 16 (bFGF mRNA). As another example, at page 64, lines 1-20, the instant specification clearly teaches comparative PCR investigation of fraction A (*i.e.*, not enriched for cancer cells) and fraction C

(*i.e.,* isolated tumor cells) for mRNA encoding MUC1, bFGF, VEGF, TIMP3, MMP2, EGP, and GAPDH.

Applicants also traverse the PTO's assertion that the specification does not adequately describe detection, in a non-cancer cell from the subject, of the second nucleic acid of step (c). Contrary to the PTO's assertion, the specification teaches such a feature, for example, at page 4, lines 24-34, a passage which concludes in pertinent part, "cancer cells removed from body fluid . . . are investigated for at least one cancer-specific gene on the basis of DNA and/or mRNA, *and the same investigation is carried out with non-cancer cells from the same individual* for comparison." (emphasis added) See also, *e.g.*, the specification at page 9, line 32 through page 10, line 7. Similarly, at, *e.g.*, page 18, line 29 through page 19, line 1, the specification describes comparing fraction A (MNC from which cancer cells have not been removed, as discussed above), fraction B (MNC after tumor cell removal) and fraction C (purified tumor cells) "with one another" and "carrying out the same investigation with non-cancer cells from the same individual for comparison. This means that the patient's own controls are included in the investigation." Additionally, for example at page 21, lines 1-7, the specification also clearly describes investigation for at least two different genes, *i.e.,* first and second nucleic acids as recited in the instant claims. Detection, in a non-cancer cell from the subject, of the second nucleic acid of step (c) is therefore clearly and unambiguously provided by the present specification as originally filed.

Accordingly, Applicants are puzzled by the PTO's assertions that the claimed invention has not been adequately described and that the claims impermissibly encompass new matter. Applicants believe the present application satisfies the written description requirement under 35 U.S.C. § 112, first paragraph,and therefore respectfully request that the rejection of these claims be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 103

I. Claims 21-22, 24-28, 32, 36-37, 41-45, 49-51, 54-59 stand rejected under 35 U.S.C. § 103. The Examiner asserts the claims are obvious over Jung et al. (*Eur. J. Clin. Chem. Clin. Biochem.* 35:3-10 (1997)) and Rimm et al. (U.S. Pat. No. 6,197,523 (March 2001)) or Ts'o et al. (U.S. Pat. No. 5,962,237 (October 1999)) in view of Hoon et al. (U.S. Pat. No.

6,057,105 (May 2000)). More specifically, the Examiner alleges that a person having ordinary skill in the art would have been motivated to combine the teachings of Jung et al. (detection of single metastatic cancer cells by RT-PCR in a peripheral blood sample) and Rimm et al. (isolating cancer cells and further characterizing them, for example, by PCR) or Ts'o et al. (removing non-rare cells from a fluid to obtain cancer cells for analysis by FISH or PCR) in view of Hoon et al. (improved sensitivity of PCR cancer detection by using multiple markers).

Applicants respectfully traverse these grounds for rejection and submit that the claimed methods would not have been obvious to a person having ordinary skill in the art at the time the application was filed. As an initial matter, and as also noted above, claims 21 and 41-43 have been canceled by the present Amendment without acquiescence and without prejudice, rendering moot the rejections of these claims.

As discussed above, Applicants' invention is directed to a method for determining an increased risk for or presence of a disseminated cancer cell or a micrometastasizing cancer cell in a body fluid from a subject. For reasons elaborated upon herein and previously made of record, the documents cited by the PTO, alone or in any combination, fail to teach or suggest the presently claimed invention.

Briefly, Jung et al. teach away from the present invention. Jung et al. merely provide a review of the state of the art with respect to RT-PCR detection of disseminated or micrometastasized cancer cells. Based on the cataloguing by Jung et al. of multiple misleading artefacts that are generated by RT-PCR laboratory procedures, these authors conclude that the question of "whether or not circulating tumor cells detected by RT-PCR have any value as prognostic markers in cancer will have to await the results of further studies", *i.e.*, that this question has <u>not</u> been resolved (Jung et al., page 5, left-hand column, lines 31-33). Jung et al., therefore, fail to provide the person skilled in the art with the requisite reasonable expectation of success, and therefore such person would <u>not</u> have been motivated to combine Jung et al. with any other teachings or suggestions from the prior art. Nowhere do Jung et al. teach or suggest the combination of steps recited in current claims 61 or 63 (which appear to be the pertinent independent base claims for the presently rejected claims), nor has the PTO established the obviousness of such combination.

Rimm et al. merely provide disclosure that is cumulative with background information provided by the present application as it relates to methods known to the art for *isolating* cancer cells from body fluids, *i.e.*, by density methods. Rimm et al. fail, however, in any way to suggest the presently claimed *method for determining* risk for or presence of a disseminated or micrometastasizing cancer cell. The primary thrust of Rimm et al. is directed at density-based isolation of cancer cells combined with *image*-based immunochemical ("epitopic") or cytological characterization of such cells. The PTO cites to a single, offhanded comment by Rimm et al. that cells processed as described therein may be used "for additional analysis by other methods such as PCR" (Action, at page 6, last three lines). Applicants submit that merely by asserting this vague allusion to the applicability of well known PCR methodology to the isolated cells of Rimm et al., the PTO falls far short of establishing that a person having ordinary skill in the art would have been motivated by Rimm et al. to combine teachings found therein with any other prior art documents, specifically to arrive at the combination of steps recited in current claims 61 or 63.

Ts'o et al. also merely provide alternative methodologies for the *isolation* of cancer cells using multiple density gradients and immobilized affinity ligand negative selection, but Ts'o et al. fail to suggest in any way the presently claimed method for determining risk for or presence of a disseminated or micrometastasizing cancer cell. As with Rimm et al., Ts'o et al. suggest that cancer cells isolated as disclosed therein may be further characterized by FISH or PCR, but Applicants submit that even given the combined teachings of the other cited documents, the PTO falls far short of establishing that Ts'o et al. suggest the specifically recited method steps of claims 61 and 63.

In particular, the documents cited by the PTO fail to contemplate the presently claimed method, wherein (a) a first nucleic acid is investigated in body fluid cells without prior removal of cancer cells (and/or the first nucleic acid is essentially not expressed in non-cancer cells); (b) cancer cells are isolated from the body fluid; (c) an isolated cancer cell is investigated for a second nucleic acid; and (d) a non-cancer cell from the body fluid is also investigated for the second nucleic acid. The present application provides for the first time this novel and nonobvious combination of method steps, and absent the disclosure of the present application the

PTO impermissibly employs hindsight in its allegation that the invention is obvious over the cited documents.

Thus, Hoon et al. also fail to remedy the deficiencies of any or all of the above cited publications. Hoon et al. merely disclose achieving enhanced sensitivity in the detection of circulating cancer cells by PCR, by teaching the use of multiple nucleic acid markers rather than single markers. The only additional suggestion by Hoon et al. for improving sensitivity in a nucleic acid-based cancer detection assay, beyond the use of multiple markers, is the use of nested oligonucleotide primers (*e.g.*, Hoon et al., Col. 18, lines 30-33). Hoon et al. nowhere, however, teach or suggest isolating a cancer cell from a body fluid and separately investigating it for a second cancer-specific or a cancer-associated nucleic acid, as a distinct step from the investigation of a first nucleic acid that is performed on an unfractionated cell population according to the claimed invention. Quite the contrary, Applicants submit that if anything, Hoon et al. teach away from doing so, and thereby teach away from the presently claimed invention, because the specific advantage to which Hoon et al. point is the increased sensitivity that is achieved by the relatively simple step of increasing the number of markers that are investigated. Moreover, any disclosures by Hoon et al. with respect to suitable biological samples are silent on the question of any type of cancer cell enrichment (Hoon et al., Col. 3, lines 27-36; Col. 4, lines 5-12), and for reasons given herein with respect both to the other publications cited by the PTO (*supra*) and to the holding of the Federal Circuit in *Rouffet* (*infra*) this deficiency of Hoon et al. is not cured merely by invoking cancer cell isolations such as those found in Rimm et al. or Ts'o et al.

Hence, a person having ordinary skill in the art would find in Hoon et al. motivation to improve the sensitivity of detection only by investigating multiple nucleic acid markers instead of a single marker, or by using nested primers, but such a skilled person would not have been motivated further to isolate a cancer cell for such investigation. Even assuming, *arguendo*, that the skilled person applied the multiple marker analysis of Hoon et al. to isolated cells of Rimm et al. or Ts'o et al., Applicants submit that the present invention would not have been achieved with the requisite reasonable expectation of success absent the teachings of the instant application, because the combined teachings of the documents cited by the PTO still fail to suggest the specifically claimed method comprising investigating (i) unfractionated body fluid

cells, (ii) cancer cells isolated therefrom, *and* (iii) non-cancer body fluid cells from the same subject, using first and second nucleic acids as recited. Because Hoon et al. absolutely fail in any way to remotely suggest any desirable modification of the teachings therein that might relate to conducting a nucleic acid analysis on an isolated cancer cell, and for reasons given above concerning the failure of the entire collection of documents cited by the Action to suggest the combination of presently claimed method steps, Applicants submit that the PTO employs impermissible hindsight using the present application, in its allegation of obviousness.

Applicants therefore respectfully submit that the documents cited by the PTO, alone or in combination, fail to teach or suggest the subject matter of the instant claims, and that the PTO has not established a *prima facie* case of obviousness. (*See In re Mayne*, 104 F.3d 133, 1341-43, 41 U.S.P.Q.2d 1451 (Fed. Cir. 1997) (PTO has the burden of showing a *prima facie* case of obviousness.)). The PTO must show (1) that the combined references teach or suggest all claim limitations; (2) that the references provide some teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce the claimed invention; and (3) that the combined teachings of the references indicate that by combining the references, a person having ordinary skill in the art will achieve the claimed invention with a reasonable expectation of success. When rejection of claims depends upon a combination of prior art references, a teaching, motivation, or suggestion to combine the references must exist. (*See In re Rouffet* , 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998)). For reasons given herein, no such teaching, motivation or suggestion to combine the references can be found in the prior art.

In particular, the Federal Circuit stated in *Roufffet* that

> "virtually all [inventions] are combinations of old elements." [cites omitted] Therefore, an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be an "illogical and inappropriate process by which to determine patentability" *Sensonics, Inc., v. Aerosonic Corp.*, 81 F.3d 1566, 1570, 38 U.S.P.Q.2d 1551, 1554 (Fed. Cir. 1996).
>
> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a

> motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

Accordingly, and for reasons provided herein and previously made of record, the PTO has failed to establish why the person having ordinary skill in the art would have selected elements from the cited prior art *in the same manner as that claimed, absent any knowledge of the presently claimed invention.*

Applicants also respectfully submit that the mere fact that the teachings of the prior art *can* be combined or modified, or that a person having ordinary skill in the art is *capable* of combining or modifying the teachings of the prior art, does not make the resultant combination *prima facie* obvious, as the prior art must also suggest the desirability of the combination (*see, e.g., In re Mills*, 16 U.S.P.Q.2d 1430, Fed. Cir. 1990; *In re Fritch*, 23 U.S.P.Q.2d 1780, Fed. Cir. 1992). Thus, applicants submit the cited references, taken alone or in combination, fail to provide any motivation or suggestion to a person of ordinary skill in the art to combine or modify the references to arrive at the claimed invention. Accordingly, applicants respectfully submit that the instant claims satisfy the requirements of 35 U.S.C. § 103 and request that these rejections be withdrawn.

II. The PTO rejects claims 29-31, 33-35, 46-48 under 35 U.S.C. § 103, asserting obviousness over Jung et al. (*Eur. J. Clin. Chem. Clin. Biochem.* 35:3-10 (1997)) and Rimm et al. (U.S. Pat. No. 6,197,523 (March, 2001)) or Ts'o et al. (U.S. Pat. No. 5,962,237 (October, 1999)) further in view of Hoon et al. (U.S. Pat. No. 6,057,105 (May, 2000)), and further in view of Schmitz et al. (U.S. Pat. No. 6,190,870 (February 2001), Popescu et al. (*Cancer Gen. Cytogenet.* 93:10-21(1997), or Torczynski it al. (U.S. Pat No. 5,589,579 (December 1996), and further in view of Hoon et al. (U.S. Pat. 6,057,105 (May 2, 2000)). The Action concedes that none of Jung et al., Rimm et al., Ts'o et al., or Hoon et al. specifically teaches the analysis of oncogenes, tumor suppressor genes, or other specifically recited genes. However, the PTO asserts that Schmitz et al. teach that tumor cells may be separated from peripheral blood by magnetic sorting, using any one of several separation markers that may be

present on the cell surface or within the cytoplasm of tumor cells. The PTO further asserts that at the time the instant application was filed, a person having ordinary skill in the art would have found it obvious to combine the teachings of Schmitz et al. to modify the method of Jung et al., Rimm et al., Ts'o et al. in view of Hoon et al. to obtain a method using any combination of markers depending upon the suspected form of cancer, or using a combination that is more applicable to cancers generically.

Applicants respectfully traverse the basis for this rejection and submit that the documents cited by the Action, alone or in combination, fail to teach or suggest the subject matter of the instant claims. As conceded by the Action, Jung et al., Rimm et al., Ts'o et al., and Hoon et al. all fail to teach the analysis of oncogenes, tumor suppressor genes, or other specifically recited genes. For reasons also discussed above with respect to Jung et al., Rimm et al., Ts'o et al., and Hoon et al., each of Schmitz et al., Popescu et al., and Torczynski et al. also fails to teach or suggest a method for determining an increased risk for or presence of a disseminated cancer cell or a micrometastasizing cancer cell, comprising the presently recited steps. Each of the cited publications also fails to teach or suggest that the first cancer-specific or cancer-associated nucleic acid is different from the second cancer-specific or cancer-associated nucleic acid. Also, none of the cited documents teaches or suggests detecting the second nucleic acid in a non-cancer cell from the subject.

For reasons previously made of record, Applicants submit that Schmitz et al. merely teach a method for enriching carcinoma cells and analyzing only the enriched fraction, to quantify the number of cancer cells present in the sample. Applicants submit that Popescu et al., Torczynski et al., and Hoon et al. all fail to remedy the deficiencies of Schmitz et al. Popescu et al. merely provide a general review of several cytogenetic methods, including FISH, for detecting chromosomal abnormalities in cancer cells. Popescu et al., alone or combined with any other documents cited by the PTO, fail to suggest the desirability of using FISH for analyzing unfractionated body fluid cells and cancer cells that have been isolated therefrom, or for analyzing disseminated or micrometastasized cells. Torczynski et al. disclose a method for diagnosing lung cancer using several markers, including several well known in the art such as CEA, NCA, and the ras and myc families of oncogenes. Torczynski et al. fail, however, to suggest any desirability of applying detection of these markers to carcinoma cells enriched

according to Schmitz et al., or to any other cell preparation method known in the art, for purposes of achieving Applicants' invention. Hoon et al. teach a method for detecting one or more markers of melanoma or breast cancer cells, but as also discussed above, Hoon et al. fail to teach or suggest detecting such markers (*e.g.*, a first marker) in body fluid cells without prior removal of cancer cells and (*e.g.*, a second marker) in cancer cells isolated from the body fluid.

Applicants submit that any combination of one or more of Jung et al., Rimm et al., Ts'o et al., Schmitz et al., Popescu et al., Torczynski et al., and Hoon et al. fails to teach or suggest all recited features of Applicants' claimed invention, particularly the investigation of cancer-specific or cancer-associated nucleic acids in both unfractionated body fluid cells and in cancer cells isolated from the body fluid of a subject, and the further investigation of a non-cancer cell from the same subject. Furthermore, alone or collectively the documents cited by the PTO fail to teach or suggest the modifications of any of the techniques disclosed therein that would be required to achieve the claimed method; nor do any of the cited documents teach or suggest the desirability of making such modifications. Applicants submit that to so modify the art could only be accomplished using impermissible hindsight in view of the instant application, for reasons discussed above. Applicants therefore submit that the claimed invention satisfies the requirements of 35 U.S.C. § 103 and respectfully request that the rejection of the claims be withdrawn.

III. Claims 38-39 and 52-53 under 35 U.S.C. § 103 stand rejected for allegedly being obvious over Mitsuhashi (U.S. Patent No. 5,976,797 (November 1999)) in view of Jung et al. and Rimm et al. or T'so et al. in view of Hoon et al., as applied above in the first basis for rejection under § 103. The PTO concedes that none of Jung et al., Rimm et al., Ts'o et al., or Hoon et al. teaches analysis or identification of an anticancer therapy by administering a therapy to samples and detecting presence or expression of markers before and after such administration. The Action, however, alleges that an ordinarily skilled artisan would have found it obvious to modify the method of Mitsuhashi for detecting cytotoxic effects of an anticancer compound by detecting multiple markers in enriched and unenriched cultures. The Action further alleges that an ordinarily skilled artisan would have been motivated to analyze more than one mRNA for reasons of specificity and reliability, as provided by Hoon et al.

Applicants respectfully traverse these grounds for rejection and submit that the subject matter of claims 38-39 and 52-53 is nonobvious. Applicants submit that Mitsuhashi, alone or in combination with Jung et al., Rimm et al., Ts'o et al., or Hoon et al., fails to teach or suggest all the limitations of the claimed invention, and further submit that none of these documents alone or in combination would have motivated a person having ordinary skill in the art to obtain Applicants' invention with a reasonable expectation of success. As the PTO concedes, Jung et al., Rimm et al., Ts'o et al., and Hoon et al. all fail to teach or suggest analyzing an anticancer therapy or identifying an anticancer therapy by detecting the presence of first and second nucleic acids before and after contacting a candidate anticancer agent with cells.

Mitsuhashi discloses a method for detecting the level of *total* mRNA isolated from cells before and after the cells are exposed to a cytotoxic agent. Mitsuhashi also teaches that the level of a specific mRNA may be measured and compared with the total mRNA from the cells. Mitsuhashi is silent, however, with respect to which *specific* mRNA might be measured and further fails to teach or suggest detecting at least one first cancer-specific or cancer-associated nucleic acid in a plurality of unfractionated cells from a body fluid of a suspected cancer patient; Mitsuhashi further fails to teach or suggest detecting a second cancer-specific or cancer-associated nucleic acid in cancer cells isolated from such a body fluid. Mitsuhashi also fails to teach or suggest detecting a cancer-related nucleic acid in non-cancer cells from such a patient, *i.e.*, a subject known to have or suspected of being at risk for having a disseminated cancer cell or a micrometastasized cancer cell.

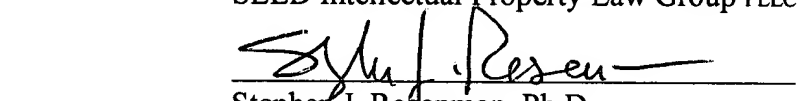
For reasons already made of record and as discussed in detail above, Jung et al., Rimm et al., Ts'o et al., and Hoon et al. all fail to teach or suggest detecting first and second nucleic acids (*e.g.*, one or more cancer-specific or cancer-associated nucleic acids) in both an unfractionated sample of body fluid cells and in a cancer cell isolated from the body fluid. Furthermore, all the cited publications fail to teach or suggest detecting the additional recited step of detecting such nucleic acids in a non-cancer cell. Applicants submit that Mitsuhashi does not teach or suggest the desirability of combining the method disclosed therein for identifying cytotoxic agents with any other method in the art for detecting disseminated or micrometastasized cells in an unfractionated body fluid cell sample, *and* with any other method for detecting disseminated or micrometastasized cells in a sample enriched for cancer cells that

have been removed from such a body fluid. Applicants further submit that, for reasons also provided above, none of the cited documents provides any motivation to combine the teachings therein, or suggestion of the desirability of making the requisite modifications to the cited disclosures, in a manner that would lead the ordinarily skilled artisan to expect reasonably to succeed in arriving at Applicants' invention.

Applicants therefore respectfully submit that a *prima facie* case of obviousness has not been set forth by the PTO, and submit that the instant claims satisfy all requirements of 35 U.S.C. § 103. Accordingly, Applicants request that the rejections of these claims be withdrawn.

Applicants respectfully submit that all claims remaining in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090. In the event that the Examiner believes a teleconference or in-person interview will facilitate prosecution of this case, the Examiner is invited to telephone the undersigned representative at 206-622-4900.

Respectfully submitted,
Michael Giesing et al.
SEED Intellectual Property Law Group PLLC



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